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The health-related quality of life and psychological profile in patients with oropharyngeal Pemphigus Vulgaris in complete clinical remission: a case-control study

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Abstract

Background: Pemphigus Vulgaris (PV) is a severe autoimmune blistering disease which may affect the patient's health related quality of life (HR-QoL) and mood even during quiescent disease activity.

We sought to evaluate HR-QoL, quality of sleep (QoS), anxiety and depression in oropharyngeal PV patients (OPV) in complete clinical remission on or off therapy (CCR-on, CCR-off).

Methods: 30 OPV patients and 30 healthy controls were enrolled. The Short Form 36 Health Survey Questionnaire (SF-36), Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Scale

(ESS), Hamilton Rating Scale for Depression (HAM-D) and Hamilton Rating Scale for Anxiety (HAM-A) were administered. Descriptive statistics, including the Mann–Whitney U test and hierarchical multiple linear regression analysis, were used.

Results: The OPV patients had statistically lower scores in the majority of items of the SF-36 and higher scores in the PSQI, HAM-A and HAM-D than the healthy controls ($p<0.004$; $p<0.001$; and $p<0.001$ respectively). Nine (30%) of the OPV patients were poor sleepers (PSQI >5) with higher scores in the SF-36, HAM-A and HAM-D compared with the good sleepers (PSQI<5). No statistically significant difference was detected in the OPV group when comparing patients in CCR-on and CCR-off, or in consideration of the cumulative time of the disease duration ~~(< 1, 1-3 and > 3 years)~~.

Conclusions: HR-QoL of OPV patients can be impaired even over periods of relatively well-being, therefore, clinicians should monitor periodically their HR-QoL, QoS and psychological profile in order to guide treatments also towards improving their HR-QoL.

Introduction

Pemphigus Vulgaris (PV) is a rare and severe autoimmune muco-cutaneous blistering disease characterized by circulating auto-antibodies targeting Desmogleins 3 and 1, which affect the mucous membranes and skin[1]. As a chronic, disabling and potentially fatal disease, PV can impair both the physical and mental health of patients affecting their HR-QoL[2].

Several studies have reported an alarming burden of the disease on the HR-QoL of PV patients, with an increasing concerns on psychological disorders[2–5]. The impact of skin and/or mucosal lesions, the chronic therapies and their related side-effects, the long-term hospitalization and the high recurrence rate can greatly impair the patients' emotions, physical health and social functioning, affecting their health status (HS)[5].

Moreover, patients with an impaired HR-QoL have an increased risk of psychiatric disorders such as anxiety and depression[3,4] and sleep disturbance (SD). Therefore, the need for objective measures to assess both HR-QoL and psychological profile in pemphigus patients has become an important aspect in relation to the monitoring of the disease[6].

Currently, several studies have shown that HR-QoL improves over the period of the treatment[2,7,8] while others have shown that HR-QoL is still impaired during quiescent periods of the disease[9]. Interestingly, although PV patients characterized by the absence of any skin or mucosal lesions have been reported to have a better HR-QoL than those with active lesions, they still present an impaired HR-QoL and high levels of anxiety and depression, despite their relative well-being when in clinical remission[9].

Although some studies have investigated the HR-QoL of PV patients, few data about the HR-QoL, quality of sleep (QoS), anxiety and depression in oropharyngeal PV (OPV) patients are available. Therefore, we decided to perform a study to evaluate the HR-QOL in OPV patients in complete clinical remission on or off therapy (CCR-on and CCR-off, respectively)[10], analyzing the role of QoS and psychological profile on the self-perception of HR-QoL. In addition, to the best of our knowledge, this will also be the first study to explore QoS in relation to PV.

Materials and Methods

Study population

A case-control study was carried out at the Oral Medicine Unit of the Federico II University of Naples in accordance with the principles of the Declaration of Helsinki and was approved by the local ethical committee (protocol number 69/19). The methods adopted conformed with the STROBE checklist and the statement for observational studies[11].

PV patients and healthy controls were consecutively screened between June 2017 and June 2019 and were frequency-matched for sex, age, and educational level. All the patients provided their written informed consent for the management of personal data before participating.

Participants of either gender and aged 18 or older were included. The inclusion criteria for the PV group were: (i) clinical findings of bullous and/or erosive lesions affecting the oropharyngeal mucosa at the time of diagnosis; (ii) histopathological findings showing intra-epithelial detachment; (iii) immunological evidence of antibody anti-Dsg 3 and anti-Dsg 1 via direct or indirect immune-fluorescence microscopy and/or enzyme-linked immunosorbent assay; (iv) patients treated only with conventional immunosuppressive

treatment (CIST) consisting of high-dose corticosteroids with or without immunosuppressants[10]; and (v) patients in CCR-on or in CCR-off according to the consensus statement on the definition of the disease[10].

Conversely, the exclusion criteria encompassed: (i) patients affected by other autoimmune bullous diseases (such as pemphigus foliaceus, or mucous membrane pemphigoid), (ii) patients treated with other therapeutic protocols rather than CIST (such as Rituximab, intravenous immunoglobulin or both); and (iii) patients with active lesions or in partial remission.

The inclusion criteria for the control group were: (i) the absence of any oral or cutaneous lesions and (ii) patients referred to the dental clinic exclusively in relation to a dental disease. The exclusion criteria encompassed: (i) patients affected by an autoimmune bullous disease or other autoimmune disease (such as Rheumatoid Arthritis, Sjogren Syndrome or Systemic Lupus Erythematous) and (ii) patients affected by debilitating condition or unstable disease (such as cancer, osteonecrosis of the jaw or dementia). For both groups, (i) participants with a medical history of a psychiatric disorder or regularly treated with a psychotropic drug, (ii) drug-addicted or alcoholic patients and (iii) patients unable to give their consent were excluded.

Data on sociodemographic characteristics, namely age, gender and occupational and marital status, together with clinical data were collected.

Questionnaires

All the participants were assessed with a predefined set of questionnaires in order to evaluate their HR-QoL, QoS, anxiety and depression levels. Three self-administered scales, namely, the Short Form 36 Health Survey Questionnaire (SF-36), used to investigate the HR-QoL [12] the Pittsburgh Sleep Quality Index (PSQI) [13] and the Epworth Sleepiness Scale (ESS)[14], used to investigate QoS, were selected. Whereas, the Hamilton Rating Scale for Anxiety (HAM-A)[15] and the Hamilton Rating Scale for Depression (HAM-D)[16], used to evaluate signs and symptoms of anxiety and depression, were administered by a single psychiatrist (P.G.) in order to reduce inter-individual variability of judgment. PSQI, ESS, HAM-A and HAM-D scales were analyzed as previously described[17]. All the questionnaires were reviewed for completeness before collection and were administered in their Italian version.

Statistical analysis

Descriptive analyses, including percentages, means, standard deviations, medians and interquartile ranges, were performed. Because of the non-normality of the data, non-parametric tests such as Mann–Whitney U-test or Kruskal-Wallis test were employed. P-values < 0.05 were considered to reflect statistical significance. Spearman rank regression analysis was performed to assess the correlation between the SF-36 items and the other clinical parameters.

A post–hoc power calculation was performed for the Mann-Whitney test. The effect size was 0.81 for a sample size of 30 participants for each group, with a significance level of 0.05. The power test value (1-Beta) was 0.92 (analysis performed via Gpower software).

A Cronbach alpha value of 0.72 was indicative of a good reliability of the PSQI scale in both groups.

Hierarchical multiple regression analyses were performed to test the importance of disease-related and psychosocial factors to the SF-36 items after checking for demographic factors. A total of six models were computed in order to test the contribution of specific variables to each SF-36 item.

The demographic model (model 1) was performed to test the contribution of the demographic variables to poor HR-QoL. Next, the QoS model (model 2), DS model (model 3), the anxiety model (model 4), the depression model (model 5), were each performed to test the contribution of the variables to poor HR-QoL after controlling for the demographic variables.

Finally, a standard regression analysis (model 6) was performed by entering all the variables simultaneously into the model in order to determine the relative contributions of these variables to the SF-36 items. All the statistical analyses were performed with the SPSS, Version 23 (IBM Inc).

Results

A total of 30 OPV patients, and 30 healthy participants were included. Their socio-demographic characteristics and clinical parameters are summarized in **Table 1**. Thirteen (43%) OPV patients were in CCR-on, while 17 (57%) were in CCR-off at the time of the study. The median duration of the PV disease was 3 years (0-11 years).

Statistically significant differences were found between the groups in relation to all the clinical parameters except for the ESS (p: 0.530). The OPV patients presented a poorer HR-QoL. The scores of the RP, GH, VT and RE were significantly lower in the OPV group ($p< 0.001$, 0.005, 0.044, 0.021 respectively). Moreover, the OPV patients showed higher median PSQI scores (p:0.004) and HAM-D and HAM-A scores ($p<0.001$) suggesting an impaired QoS and mood with respect to the healthy subjects **(Table 1)**.

Specifically, 9 (30.0%) OPV patients, 5 (16.7%) in CCR-on and 4 (13.3%) in CCR-off, presented with sleep disturbances (SD). Anxiety was present in 18 cases (60.0%; 23.3% mild, 26.7% moderate and 10.0% severe), whereas depression was reported in 15 cases (50.0%; 33.3% mild, 13.4% moderate and 3.3% severe). Conversely, 3 (10.0%) healthy participants presented SD, 7 (23.3%) mild anxiety levels, and none depression.

~~Differences between medians were observed~~ When differentiating the OPV patients by gender~~. In detail,~~ we found that the female patients presented lower median scores for the majority of the SF-36 components, although a statistically significant difference was observed only for the MH component (p: 0.017). Also, the female patients presented significantly higher median scores for both the HAM-A and HAM-D (p: 0.022, 0.038) suggesting that women are at a higher risk of mood disorders than men. On the contrary, no differences were observed in terms of the PSQI and ESS (p: 0.902, 0.157), indicating that QoS may not be influenced by gender.

~~**Table 3** shows~~ Moreover, no statistically significant differences were found between patients in CCR-on and CCR-off, nor significant correlations with respect to disease duration for none of the clinical variables. ~~The variations of the clinical variables the OPV~~

patients with respect to different disease duration and in CCR-on and CCR-off therapy were also analyzed. For statistical purposes, the duration of the disease was categorized into three sub-groups (<1, n:8; 1-3 n:13; and >3years n:9). No statistical significant difference was found in the SF-36 items, PSQI, HAM-D, HAM-A and ESS scores (p: 0.240, 0.188, 0.175 and 0.808 respectively).

Table 2 presents a correlation analysis between each item of the SF- 36, PSQI, HAM-D, HAM-A and ESS in the OPV group. PF, BP, VT and SF showed a strong negative correlation with the global score of the PSQI ($p < 0.001$, <0.001, 0.008 and 0.002 respectively). BP, GH, SF and MH were negatively and strongly correlated with the total score of the HAM-A ($p < 0.001$, 0.007, <0.001 and <0.001 respectively). BP, VT, SF, RE and MH were negatively and strongly correlated with the total score of the HAM-D ($p < 0.001$, 0.010, <0.001, 0.009, and <0.001 respectively). Overall, as the SF-36 scores decreased, the scores of the HAM-D and HAM-A increased, suggesting that a poorer QoS and higher anxiety and depression levels correspond with a worse HR-QoL.

Among the OPV patients, the clinical parameters of good (PSQI ≤ 5) and poor (PSQI>5) sleepers were also compared **(Table 3)**. PF, RP, BP, VT, SF and MH were statistically significantly different between the poor and good sleepers, as well as HAM-A and HAM-D scores ($p<0.001$; p: 0.007) suggesting that the poor sleepers had a greater impairment of their HR-QoL and higher level of anxiety and depression. On the contrary no differences were detected with respect to DS (ESS) (p: 0.369).

Hierarchical multiple regression analyses predicting the HR-QoL are shown in **Table 4**. The first model (the demographic model) testing the contribution of the demographic variables to each SF-36 item was found to be not statistically significant except for MH (R2 = 26.6, p: 0.018).

The addition of QoS (model 2) resulted in a strongly significant increase in the R2 value for PF, BP, VT, SF and MH ($\Delta R2$ = 23.2%, p:0.005; 40.5%, $p<0.001$; 30.2%; p <0.001; 37.5%; $p<0.001$; and 20.2%, p:0.003), and a moderately significant increase for GH ($\Delta R2$= 14.5%, p:0.020). Whereas, in the model 3, only a moderately significant increase in the R2 value was found for VT ($\Delta R2$= 14.6%, p:0.025).

The addition of anxiety (model 4) resulted in a strongly significant increase in the R2 value for the items PF, GH and VT ($\Delta R2$=25.9%, p:0.003; 27.6%, $p<0.001$; and 36.0%;

p<0.001 respectively), and a moderately significant increase for the item RE (ΔR2= 14.8%, p:0.025).

The addition of depression (model 5) resulted in a strongly significant increase in the R2 value for the items of PF, VT, and SF (ΔR2 = 29.4%, p<0.001; 35.5%, p<0.001; and 36.5%, p<0.001; respectively) and a moderately significant increase for the items of RP, GH and RE (ΔR2 = 11.9%, p:0.037; 13.2%, p:0.025; and 12.6%, p:0.036 respectively).

Model 6 (the final full model), in which all of the variables were entered simultaneously, could explain from 12.5% up to 66.5% of the variance in the SF-36 items.

Discussion

Physical and mental health can be seriously compromised in PV patients~~, especially those with a recent disease onset and a more clinically severe diagnosis~~[4,18] even over periods of relative well-being [9].

~~In this regard, some studies have reported a poor HR-QoL in PV patients, strongly associated with anxiety and depression disorders~~[2–4,18,19]~~. Despite the fact that a worsening in the HR-QoL has been mainly reported in patients with an active disease~~ [2,4,9,20]~~, Tabolli et al~~

~~in their study observed an impairment of the HR-QoL in 47 patients with muco-cutaneous PV while in CCR~~[9]. ~~Similarly,~~ In the present study, the OPV patients in CCR showed a poorer HR-QoL compared with the healthy population. In particular, the patients reported a limitation in their work and daily activities resulting from the low scores in their self-perception of their physical and emotional health (items RP and RE) with a reduction in their vitality and general health.

These results suggest that the burden of the disease may be present regardless of the positive clinical outcomes achieved, findings which have been further confirmed by the regression analysis. Similarly, data from a meta-analysis of 5 studies assessing HR-QoL in PV patients by using the SF-36, have highlighted that overall PV patients presented the highest impairment in the RF dimension followed by RE and VT, pointing out that these three dimensions may be the most affected in PV patients[21].

Moreover, a high prevalence of psychiatric distress was also detected in our sample. Anxiety and depression were found in 60.0% and 50.0% of the OPV patients, especially in females, who experienced higher levels of mood disorders than males, in line with findings from other reports[22,23].

In the literature, a high variability in the prevalence of mood disorders (33.6 -74%) has been reported, possibly due to the heterogeneity of the studied populations who presented with very different levels of disease activity[3,7,18–20].

Besides, the majority of these studies have reported a negative correlation between the HR-QoL and psychiatric comorbidities[2–4,9,20]. Likewise, in our population, anxiety and depression were all negatively correlated with the HR-QoL.

The novelty of this study has been the evaluation of QoS in PV patients as an adjunct to the HR-QoL assessment. In our population, 30.0% of the OPV patients were poor sleepers and presented with higher levels of anxiety and depression and a worse HR-QoL compared with the good sleepers, suggesting a strong association among these conditions in OPV patients also in CCR.

In contrast to anxiety and depression, QoS was not influenced by gender, as further confirmed by the regression analysis. This result highlights the importance of assessing also QoS of OPV patients, as the presence of SD may be *per se* indicative of a worsening in the HR-QoL or the presence of mood alterations. Indeed, the association between SD and psychiatric disorders, for instance anxiety and depression, is well established in the

literature[24]. Moreover, SD are recognized to be risk factors for the onset of psychiatric disorders[24] or their recurrence[24,25].

A bidirectional relationship has been reported between sleep and autoimmunity. For instance, IL-6 has been demonstrated to be higher in sleep-deprived individuals and PV patients have been found to have higher levels of the IL-6 serum concentration both in the active and remission phase of the disease[26]. Moreover, it has been suggested that sleep deprivation may be associated with the onset of PV by suppressing the activity of the nTreg cells, which modulate the T cell proliferation and whose role is pivotal for the prevention of autoimmunity[26]. Significantly, also depression and SD may have a mutual relationship, as one is a risk factor for the other, and vice versa [24].

It is worth noting that 13 of our patients in CCR-on were by definition on minimal therapy[10] and this *per se* might have affected their HS. Nevertheless, no differences were detected between the patients off or on therapy for any of the variables assessed. However, data on the role of steroid therapy in altering HR-QoL[4,20] and mood[5] are heterogeneous and controversial in the literature and no robust conclusion could be drawn with this respect.

Moreover, in our sample, the duration of the disease was not found to be a risk factor for physical and mental health, as also reported previously[4,18,20], in contrast with the finding of a worse HS in patients with a duration of the disease longer than 5 years or with a recent onset (less than 2 years)[2].

According to the hierarchical multiple regression analyses, a strong association between the HR-QoL, mood disorders and SD, regardless of the CCR status, has been observed, considering that the final full model could explain up to 66.5 % of the variation in the SF-36 items.

Therefore, the impairment of the HR-QoL could be related to many factors, for instance, the chronicity of the disease, the difficulty in the treatment, the application of immunosuppressive therapies, the possible iatrogenic comorbidities of high-dose corticosteroid, or the patients' experience of the disease itself.

Another interesting factor is the potential correlation between autoimmune diseases and depression-like symptoms. Indeed, autoimmune diseases have been associated with psychological symptoms, such as fatigue, reduced appetite, apathy, decreased social interaction, impaired concentration, loss of interest in daily activities and SD. These

symptoms, potentially induced by systemic inflammation and often described as a sickness behavior, are also core symptoms in the diagnosis of mood disorders and an altered HR-QoL. Changes in the sickness behavior may be produced by the effect of pro-inflammatory molecules on the Central Nervous System by altering the tryptophan-kynurenine pathway, which regulates serotonin production and N-methyl-D-aspartate glutamate receptor activity[27]. Moreover, activation of the immune system increases the activity of the hypothalamic-pituitary-adrenal axis, which is known to be involved in mood disorders[27]. While the hypothesis of a cause-effect relationship between immunity and mood disorders is interesting, it remains unclear how brain functions are influenced by immunological processes, or whether other potential factors such as genetic, psychological, non-immune-related mechanisms may be involved[28].

Overall, our results should be interpreted cautiously due to some limitations. First, the nature of the study design makes inappropriate to draw any robust cause-effect relationship between poor HR-QoL and QoS and psychiatric comorbidities or with regard to disease duration or minimal therapy on account of small sample size of the subgroups compared.

Another limitation is the absence of any disease specificity in relation to the set of questionnaires selected. These tools were chosen for two reasons. First, the requirement to compare a sample of patients in relatively good health with a healthy control group made the choice of disease-specific questionnaires unfeasible. Secondly, the Autoimmune Bullous Disease Quality of Life and Treatment of Autoimmune Bullous Disease Quality of Life questionnaires [29,30] have not yet been validated in Italian.

~~Nevertheless, our findings may suggest that OPV patients, even if in CCR, could present HR-QoL impairment, along with sleep and mood disorders.~~

Conclusion

Our findings suggest that OPV patients, even if in CCR, could present HR-QoL impairment along with sleep and mood disorders, although no conclusive relationship could be deduced due the relative small sample size and the non-specificity of the questionnaires administered.

Clinicians should take into account the impact of the disease on the HR-QoL of OPV patients and should periodically monitor also their psychological profile as OPV patients may be at risk of physical and mental health impairment even during periods of relative well-being. Besides, PV patients should be carefully assessed with respect to their HS also in CCR because the persistence of a poor HR-QoL and higher levels of anxiety and depression is considered as a risk factor for a relapse of the disease[26].

Prospective longitudinal studies are needed in order to evaluate comprehensively the course of the disease in relation to HR-QoL, QoS and mood disorders.

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Tables

Table 1. Demographic and clinical characteristics of the PV group and control group.

	PV group	**Control group**	*p*-value
Demographic variables	**Mean - SD**	**Mean - SD**	
Age	51.50+/-13.25	53.63+/-12.78	0.403
Years of education	11.87+/-4.15	12.40+/-2.95	0.765
Gender	Male: Female 13:17	Male: Female 13:17	-
Marital status	Married: Unmarried 21:9	Married: Unmarried 24:6	-
Full-time employment	Yes: No 18:12	Yes: No 15:15	-
CIST		-	-
Steroids only	6 (20.0%)	-	-
Steroids + AZA	24 (80.0%)	-	-
Duration (months)	30.4 +/-25.3	-	-
CCR-on	13 (43.3%)	-	-
CCR-off	17 (56.6%)	-	-
Clinical parameters	**Median [IQR]**	**Median [IQR]**	
SF-36 items:			
PF	100 [83.75-100]	100 [98,75-100]	0.078
RP	75 [25-100]	100 [100-100]	**<0.001****
BP	92 [51.75-100]	100 [84-100]	0.057
GH	63 [50.25-82]	82 [67-90]	**0.005****
VT	65 [53.75-80]	75 [60-90]	**0.044***
SF	87 [62-100]	93,5 [87-100]	0.099
RE	100 [33-100]	100 [66-100]	**0.021***
MH	72 [58-84]	80 [72-84]	0.111
PSQI	4.0 [2.75- 6]	2.0 [1-4]	**0.004****
ESS	2.0 [0-4]	2.0[1-5]	0.530
HAM-A	12.5 [6.75-20.5]	3.0 [0.75-10,25]	**<0.001****
HAM-D	9.0 [5.75-14]	5.0 [0-4]	**<0.001****

Legend: **AZA**= azathioprine; **BP**= Bodily Pain**; CCR-on**= complete clinical remission on therapy; **CCR-off**= complete clinical emission off therapy; **CIST**: conventional

immunosuppressive therapy; **ESS**= Epworth Sleepiness Scale; **GH**= general health; **HAM-A**= Hamilton Anxiety Scale; **HAM-D**= Hamilton Depression Scale, **IQR**= interquartile range; **MH**= mental health; **PF**= physical functioning; **PSQI**=Pittsburgh Sleep Quality Index; **RE**=emotional role; **RP**= physical role; **SD=** standard deviation**; SF**= social functioning; **SF-36**= Short Form 36 Health Survey Questionnaire **VT**= vitality

The significance difference between medians was measured by the Mann–Whitney U-test. *Moderately significant $0.01 < P \leq 0.05$; **strongly significant $P \leq 0.01$.

Table 2. Correlation analysis between the SF-36 items and other clinical parameters in the PV patients.

SF-36	**PSQI**		**ESS**		**HAM-A**		**HAM-D**	
	Rho	***p-value***	**Rho**	***p-value***	**Rho**	***p-value***	**Rho**	***p-value***
PF	-,642	**<0.001****	-,109	0.568	-,298	0.109	-,319	0.086
RP	-,314	0.091	-034	0.857	-,357	0,053	-,399	**0.029***
BP	-,620	**<0.001****	-,230	0.221	-,696	**<0.001****	-,691	**<0.001****
GH	-,308	0.098	-,076	0.690	-,479	**0.007****	-,374	**0.042***
VT	-,473	**0.008****	-,161	0.395	-,403	**0.027***	-,465	**0.010****
SF	-,536	**0.002****	-,142	0.455	-,726	**<0.001****	-,616	**<0.001****
RE	-,264	0.158	,103	0.589	-,422	0.020	-,471	**0.009****
MH	-,380	**0.038***	-,021	0.911	-,702	**<0.001****	-,602	**<0.001****

Legend: **BP**= Bodily Pain; **ESS**= Epworth Sleepiness Scale; **GH**= general health; **HAM-A**= Hamilton Anxiety Scale; **HAM-D**= Hamilton Depression Scale, **IQR**= interquartile range; **MH**= mental health; **PF**= physical functioning; **PSQI**=Pittsburgh Sleep Quality Index; **RE**=emotional role; **RP**= physical role; **SD=** standard deviation**; SF**= social functioning; **SF-36**= Short Form 36 Health Survey Questionnaire **VT**= vitality

Correlation between SF-36 items and other variables was measured with the Spearman correlation analysis.

*Moderately significant $0.01 < P \leq 0.05$; **strongly significant $P \leq 0.01$.

Table 3 Comparison between the Good and Poor sleepers among the PV patients**.**

	PSQI ≤ 5 (n=21)	**PSQI >5 (n=9)**	***p-value***
	Median [IQR]	**Median [IQR]**	
SF-36			
PF	100 [97-100]	85 [45-97.5]	**0.003****
RP	75 [50-75]	25 [0-87.5]	**0.029***
BP	100 [78-100]	41 [31-72.5]	**<0.001****
GH	65 [56-82]	45 [20-78.5]	0.066
VT	65 [62.5-80]	35 [27.5-62.5]	**0.005****
SF	87 [75-100]	50 [37-93.5]	**0.015***
RE	100 [33-100]	33 [0-100]	0.075
MH	76 [66-86]	52 [22-66]	**0.005****
ESS	2.0 [0-3]	4.0 [0.5-5.5]	0.369
HAM-A	9.0 [6-14.5]	24.0 [15.5-26.5]	**0.007****
HAM-D	7.0[4-10.5]	15.0 [11-22]	**<0.001****

Legend: **BP**= Bodily Pain; **ESS**= Epworth Sleepiness Scale; **GH**= general health; **HAM-A**= Hamilton Anxiety Scale; **HAM-D**= Hamilton Depression Scale, **IQR**= interquartile range; **MH**= mental health; **PF**= physical functioning; **PSQI**=Pittsburgh Sleep Quality Index; **RE**=emotional role; **RP**= physical role; **SD=** standard deviation**; SF**= social functioning; **SF-36**= Short Form 36 Health Survey Questionnaire **VT**= vitality

The significance difference between medians was measured by the Mann–Whitney U-test. Moderately significant $0.01 < P \leq 0.05$, strongly significant $P \leq 0.01$.

Table 4. Multiple linear regression model predicting QoL in the OPV patients.

Physical Functioning												
Predictors	**Model 1**		**Model 2**		**Model 3**		**Model 4**		**Model 5**		**Model 6**	
	Beta (SE)	**P-value**	**Beta (SE)**	**P-value**	**Beta (SE)**	**P-value**	**Beta (SE)**	**P-value**	**Beta (SE)**	**P-value**	**Beta (SE)**	**P-value**
Age	-0.62 (0.3)	0.072	-0.67 (0.3)	0.021*	-0.61 (0.3)	0.040*	-0.16 (0.3)	0.613	-0.65 (0.3)	0.064	-0.43 (0.3)	0.248
Gender: F	-10.2 (7.5)	0.188	-1.39 (6.7)	0.837	-0.64 (7.1)	0.928	-4.62 (6.8)	0.504	-11.5 (7.8)	0.155	0.21 (7.7)	0.978
Years of education	-0.75 (1.0)	0.461	-0.97 (0.8)	0.260	-1.12 (0.86)	0.2079	-0.53 (0.9)	0.546	-0.84 (1.0)	0.421	0.80 (0.9)	0.383
Marital status: Married	9.89 (7.7)	0.209	7.13 (6.4)	0.276	7.35 (6.6)	0.274	5.71 (6.8)	0.408	10.5 (7.8)	0.189	5.47 (6.8)	0.430
Quality of sleep (PSQI)			-3.66 (1.2)	0.005**							-1.68 (1.7)	0.334
Daytime sleepiness (ESS)					-0.80 (1.1)	0.480					0.43 (1.0)	0.678
Anxiety (HAM-A)							-1.34 (0.4)	0.003**			-0.21 (0.9)	0.820
Depression (HAM-D)									-1.77(0.5)	0.0017**		0.297
***Adj* R^2 (%)**	**6.5**	**0.230**	**29.7**	**0.017***	**4.6**	**0.303**	**32.4**	**0.011***	**35.9**	**0.006****	**31.3**	**0.034***
***R^2change* (%)**			**23.2**	**0.005****	**-1.9**	**0.480**	**25.9**	**0.003****	**29.4**	**<0.001****	**24.8**	**0.031***
Role Physical												
Predictors	**Model 1**		**Model 2**		**Model 3**		**Model 4**		**Model 5**		**Model 6**	
	Beta (SE)	**P-value**	**Beta (SE)**	**P-value**	**Beta (SE)**	**P-value**	**Beta (SE)**	**P-value**	**Beta (SE)**	**P-value**	**Beta (SE)**	**P-value**
Age	−1.5 (0.6)	0.018*	−1.62 (0.5)	0.009**	−1.53 (0.6)	0.014*	−1.02(0.6)	0.139	−1.66 (0.6)	0.012**	−1.52 (0.7)	0.059
Gender: F	-33.0(13.9)	0.026*	−21.5(14.0)	0.136	−21.13(14.5)	0.159	-26.53(14.0)	0.069	−37.48(14.1)	0.013**	−25.86(16.3)	0.127

Years of education	−2.5 (1.8)	0.188	−2.79 (1.7)	0.121	−2.97 (1.7)	0.108	−2.27 (1.8)	0.220	−2.80 (1.8)	0.141	−2.77 (1.9)	0.160
Marital status: Married	6.7 (14.1)	0.638	3.15 (13.3)	0.814	3.58 (13.5)	0.793	1.94 (13.9)	0.890	8.85 (14.0)	0.533	4.03 (14.3)	0.782
Quality of sleep (PSQI)			−4.19 (2.4)	0.102							−1.18 (3.5)	0.744
Daytime sleepiness (ESS)					−2.75 (2.0)	0.185					−1.57 (2.1)	0.480
Anxiety (HAM-A)							−1.66 (0.8)	0.061			0.28 (1.9)	0.886
Depression (HAM-D)									−2.29 (1.0)	0.037*	−1.98 (2.2)	0.384
***Adj R^2* (%)**	**15.9**	**0.078**	**21.8**	**0.049***	**18.8**	**0.072**	**24.5**	**0.035***	**27.2**	**0.024***	**19.3**	**0.119**
***R^2change* (%)**			**5.9**	**0.102**	**2.9**	**0.185**	**8.6**	**0.061**	**11.9**	**0.037***	**3.4**	**0.316**
Bodily Pain												
Predictors	**Model 1**		**Model 2**		**Model 3**		**Model 4**		**Model 5**		**Model 6**	
	Beta (SE)	**P-value**	**Beta (SE)**	**P-value**	**Beta (SE)**	**P-value**	**Beta (SE)**	**P-value**	**Beta (SE)**	**P-value**	**Beta (SE)**	**P-value**
Age	-035 (0.5)	0.458	-0.45(0.3)	0.138	-0.32 (0.3)	0.252	0.44 (0.4)	0.288	-0.42 (0.46)	0.367	-0.19 (0.35)	0.594
Gender: F	-14.1(10.6)	0.198	2.64 (7.2)	0.716	5.64 (6.9)	0.427	-4.32 (8.5)	0.617	-17.1 (10.8)	0.124	7.03 (7.5)	0.364
Years of education	0.37 (1.4)	0.792	-0.02(0.8)	0.982	-0.37 (0.8)	0.666	0.75 (1.1)	0.499	0.17 (1.4)	0.901	-0.08 (0.8)	0.927
Marital status: Married	12.2(10.7)	0.266	7.02 (6.8)	0.313	7.01 (6.4)	0.290	4.99 (8.5)	0.563	13.3 (10.7)	0.212	5.18 (6.7)	0.447
Quality of sleep (PSQI)			-6.36(1.5)	0.003**							−1.29 (1.6)	0.448
Daytime sleepiness (ESS)					-1.93 (1.5)	0.222					0.59 (1.0)	0.568
Anxiety							-2.7 (0.4)	<0.001			−1.62 (0.9)	0.089

(HAM-A)												
Depression (HAM-D)									-3.35 (0.5)	<0.001	−1.32 (1.0)	0.218
***Adj* R^2 (%)**	**-1.2**	**0.473**	**39.3**	**0.003****	**0.9**	**0.408**	**63.7**	**<0.001****	**59.9**	**<0.001****	**63.5**	**<0.001****
***R^2change* (%)**			**40.5**	**<0.001****	**-0.3**	**0.222**	**64.9**	**<.0.001****	**61.1**	**<.0.001****	**64.7**	**<.0.001****
General Health												
Predictors	**Model 1**		**Model 2**		**Model 3**		**Model 4**		**Model 5**		**Model 6**	
	Beta (SE)	**P-value**	**Beta (SE)**	**P-value**	**Beta (SE)**	**P-value**	**Beta (SE)**	**P-value**	**Beta (SE)**	**P-value**	**Beta (SE)**	**P-value**
Age	−0.35 (0.4)	0.364	−0.39 (0.3)	0.269	−0.33 (0.3)	0.293	0.09 (0.4)	0.803	-0.39 (0.39)	0.325	−0.16 (0.4)	0.693
Gender: F	−16.10 (8.6)	0.075	−8.55 (8.5)	0.328	−4.39 (7.8)	0.581	−10.59(8.2)	0.208	-17.6 (9.00)	0.062	−2.58 (8.8)	0.772
Years of education	−1.08 (1.1)	0.357	−1.26 (1.1)	0.246	−1.53 (0.9)	0.124	−0.87 (1.0)	0.417	-1-18 (1.17)	0.325	−1.47 (1.0)	0.168
Marital status: Married	14.22 (8.7)	0.118	11.85 (8.1)	0.157	11.11 (7.3)	0.140	10.11 (8.1)	0.227	14.9 (8.93)	0.107	10.06 (7.7)	0.210
Quality of sleep (PSQI)			−3.60 (1.4)	0.020*							−0.82 (1.9)	0.674
Daytime sleepiness (ESS)					-0.92(1.28)	0.477					0.711 (1.1)	0.554
Anxiety (HAM-A)							−1.64 (0.4)	<0.001**			−2.38 (1.0)	0.035*
Depression (HAM-D)									−1.51 (0.6)	0.025*	1.18 (1.2)	0.340
***Adj* R^2 (%)**	**12.6**	**0.126**	**27.1**	**0.024***	**10.3**	**0.180**	**40.2**	**0.003****	**25.8**	**0.029***	**35.7**	**0.020***
***R^2change* (%)**			**14.5**	**0.020***	**-2.3**	**0.477**	**27.6**	**<0.001****	**13.2**	**0.025***	**23.1**	**0.029***
Vitality												
Predictors	**Model 1**		**Model 2**		**Model 3**		**Model 4**		**Model 5**		**Model 6**	
	Beta (SE)	**P-value**	**Beta (SE)**	**P-value**	**Beta (SE)**	**P-value**	**Beta (SE)**	**P-value**	**Beta (SE)**	**P-value**	**Beta (SE)**	**P-value**

Age	−0.69 (0.4)	0.069	−0.76 (0.3)	0.014*	−0.68 (0.3)	0.025*	−0.12 (0.3)	0.709	−0.80 (0.3)	0.026*	−0.54 (0.3)	0.139
Gender: F	−7.14 (8.3)	0.399	3.49 (7.0)	0.624	5.12 (7.2)	0.481	−0.18 (7.1)	0.979	−11.49 (7.8)	0.157	0.80 (7.5)	0.916
Years of education	−2.11 (1.1)	0.069	−2.36 (0.9)	0.012*	−2.58 (0.9)	0.007**	−1.84 (0.9)	0.055	−2.39 (1.0)	0.028*	−2.34 (0.8)	0.014*
Marital status: Married	8.23 (8.4)	0.339	4.91 (6.7)	0.469	4.98 (6.6)	0.461	3.05 (7.1)	0.670	10.30 (7.8)	0.199	4.97 (6.6)	0.463
Quality of sleep (PSQI)			−4.54 (1.2)	<0.001**							−1.87 (1.6)	0.273
Daytime sleepiness (ESS)					−2.68 (1.1)	0.025*					−1.36 (1.0)	0.191
Anxiety (HAM-A)							−1.72 (0.4)	<0.001**			−0.30 (0.9)	0.736
Depression (HAM-D)									−2.13 (0.5)	<0.001	−1.02 (1.0)	0.335
***Adj* R^2 (%)**	**7.4**	**0.210**	**37.6**	**0.004****	**22.0**	**0.048***	**43.4**	**<0.001****	**42.9**	**<0.001****	**46.4**	**0.004****
***R^2change* (%)**			**30.2**	**<0.001****	**14.6**	**0.025***	**36**	**<0.001****	**35.5**	**<0.001****	**39.0**	**0.003****
Social Functioning												
Predictors	**Model 1**		**Model 2**		**Model 3**		**Model 4**		**Model 5**		**Model 6**	
	Beta (SE)	**P-value**	**Beta (SE)**	**P-value**	**Beta (SE)**	**P-value**	**Beta (SE)**	**P-value**	**Beta (SE)**	**P-value**	**Beta (SE)**	**P-value**
Age	-0.01 (0.4)	0.977	-0.07 (0.3)	0.811	0.006 (0.3)	0.982	0.63 (0.3)	0.086	-0.09 (0.4)	0.807	0.25 (0.4)	0.506
Gender: F	-11.9 (8.9)	0.196	-0.83 (7.7)	0.914	2.47 (7.1)	0.733	-4.02 (7.4)	0.592	-15.3 (8.9)	0.097	0.97 (8.0)	0.904
Years of education	0.68 (1.2)	0.572	0.42 (0.9)	0.665	0.13 (0.8)	0.878	0.99 (0.9)	0.310	0.46 (1.1)	0.694	0.38 (0.9)	0.685
Marital status: Married	8.36 (9.1)	0.366	4.90 (7.3)	0.515	4.54 (6.6)	0.502	2.48 (7.4)	0.739	10.0 (8.8)	0.269	3.50 (7.0)	0.626
Quality of sleep (PSQI)			-5.15 (1.3)	<0.001**							-2.13 (1.7)	0.241
Daytime sleepiness (ESS)					-2.13 (1.3)	0.107					-0.35 (1.1)	0.747

Anxiety (HAM-A)							-2.02 (0.4)	<0.001**			-1.44 (0.9)	0.150*
Depression (HAM-D)									-2.2 (0.5)	<0.001**	0.01 (1.1)	0.992
***Adj* R^2 (%)**	**-2.7**	**0.532**	**34.8**	**0.007****	**4.1**	**0.316**	**45.4**	**<0.001****	**33.8**	**0.009****	**42.0**	**0.008****
***R^2change* (%)**			**37.5**	**<0.001****	**6.8**	**0.107**	**48.1**	**<0.001****	**36.5**	**<0.001****	**44.7**	**0.002****
Emotional Role												
Predictors	**Model 1**		**Model 2**		**Model 3**		**Model 4**		**Model 5**		**Model 6**	
	Beta (SE)	**P-value**	**Beta (SE)**	**P-value**	**Beta (SE)**	**P-value**	**Beta (SE)**	**P-value**	**Beta (SE)**	**P-value**	**Beta (SE)**	**P-value**
Age	0.68 (0.7)	0.344	-0.76 (0.6)	0.260	-0.66 (0.6)	0.318	−0.15(0.7)	0.844	−0.69 (0.7)	0.353	−0.70 (0.8)	0.426
Gender: F	−28.2 (16.1)	0.092	-15.0 (16.1)	0.361	-12.1 (16.3)	0.463	−21.8(16.4)	0.196	−28.5 (16.9)	0.104	−5.92 (18.4)	0.751
Years of education	−0.23 (2.1)	0.915	−0.54 (2.0)	0.788	−0.84 (1.9)	0.675	0.02(2.1)	0.992	−0.25 (2.2)	0.910	−0.76 (2.1)	0.725
Marital status: Married	22.6 (16.3)	0.178	18.5 (15.3)	0.238	18.4 (15.1)	0.235	17.8 (16.3)	0.285	22.8 (16.8)	0.187	16.4 (16.3)	0.325
Quality of sleep (PSQI)			−4.22 (2.9)	0.157							0.78 (4.0)	0.843
Daytime sleepiness (ESS)					−0.18 (2.4)	0.938					2.11 (2.4)	0.403
Anxiety (HAM-A)							−2.26 (0.9)	0.025*			−2.28 (2.2)	0.316
Depression (HAM-D)									−2.6 (1.2)	0.037*	−0.78 (2.5)	0.761
***Adj* R^2 (%)**	**5.5**	**0.257**	**9.5**	**0.195**	**1.5**	**0.391**	**20.3**	**0.060**	**18.1**	**0.078**	**12.5**	**0.208**
***R^2change* (%)**			**4.0**	**0.157**	**-4.0**	**0.938**	**14.8**	**0.025***	**12.6**	**0.036***	**7.0**	**0.234**
Mental Health												
Predictors	**Model 1**		**Model 2**		**Model 3**		**Model 4**		**Model 5**		**Model 6**	
	Beta (SE)	**P-value**	**Beta (SE)**	**P-value**	**Beta (SE)**	**P-value**	**Beta (SE)**	**P-value**	**Beta (SE)**	**P-value**	**Beta (SE)**	**P-value**

Age	−0.24 (0.3)	0.440	−0.30 (0.2)	0.192	−0.23 (0.2)	0.274	0.21(0.3)	0.489	−0.27 (0.3)	0.394	−0.19 (0.3)	0.488
Gender: F	−17.6 (7.1)	0.020*	−7.59 (5.5)	0.186	−5.13 (5.1)	0.331	−12.07(6.3)	0.067	−18.9 (7.4)	0.017*	−2.58 (5.7)	0.658
Years of education	−0.83 (0.9)	0.392	−1.07 (0.6)	0.134	−1.31 (0.6)	0.049*	−0.61(0.8)	0.456	−0.91 (0.9)	0.355	−1.21 (0.6)	0.086
Marital status: Married	16.83 (7.2)	0.028	13.68 (5.2)	0.016	13.51 (4.8)	0.009**	12.66 (6.2)	0.055	17.44 (7.3)	0.026*	12.31 (5.08)	0.024*
Quality of sleep (PSQI)			−3.66 (1.1)	0.003**							−0.15 (1.2)	0.902
Daytime sleepiness (ESS)					−0.79 (1.0)	0.464					0.90 (0.7)	0.254
Anxiety (HAM-A)							−1.76 (0.3)	<0.001**			−1.58 (0.7)	0.032*
Depression (HAM-D)									−2.02 (0.4)	<0.001**	−0.41 (0.8)	0.601
***Adj R^2* (%)**	**26.6**	**0.018***	**47.2**	**<0.001****	**25.2**	**0.032***	**68.2**	**<0.001****	**61.6**	**<0.001****	**66.5**	**<0.001**
***R^2change* (%)**			**20.2**	**0.003****	**-1.4**	**0.464**	**41.6**	**<0.001****	**35.0**	**<0.001****	**39.1**	**<0.001**

Legend: **Adj R^2**= adjusted R^2; **ESS**= Epworth Sleepiness Scale; **HAM-A**= Hamilton Anxiety Scale; **HAM-D**= Hamilton Depression Scale, **IQR**= interquartile range; **OPV=** oropharyngeal Pemphigus Vulgaris; **PSQI**=Pittsburgh Sleep Quality Index; **SF-36**= Short Form 36 Health Survey Questionnaire.

SE are the standard errors of beta estimates. P-values were obtained by the hypothesis test on regression coefficients. *Moderately significant $0.01 < P \leq 0.05$; **strongly significant $P \leq 0.01$.